REMARKS

I. Status of Claims

Currently, claims 1-40 are pending in this application. Claims 12, 14, 16-18, 21-24, and 31-39 have been withdrawn from consideration by the Office as directed to non-elected inventions. Claims 1-11, 13, 15, 19, 25-30, and 40 stand rejected.

By this Amendment, Applicant proposes to cancel claims 11, 19, 20, and 30 without prejudice or disclaimer, amend claims 28 and 29, and add claim 41. Support for this amendment can be found throughout the specification, including, for example, at page 11, lines 3-24. Accordingly, the proposed amendment does not introduce new matter.

Applicant respectfully requests that the Examiner enter this Amendment under 37 C.F.R. § 1.116, placing the pending claims in condition for allowance. Applicant submits that the proposed amendments of claims 28 and 29 and addition of claim 41 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, because all of the elements and their claimed relationships were either claimed earlier or inherent in the claims as examined. New claim 41, depends from claim 29 and recites that the activity "is extension time in a PCR reaction," as currently recited in claim 29. Therefore, this Amendment should allow for immediate action by the Examiner. Furthermore, the proposed amendment would place the claims in better form for appeal, should an appeal be necessary.

II. Objection to the Specification

The Office maintained the objection to the specification asserting that "the trademark DEEP VENT® needs to be capitalized." Office Action at 2. Applicant respectfully traverses this objection.

As noted in the M.P.E.P., "the use of trademarks having definite meanings is permissible in patent applications . . . . Trademarks should be identified by capitalizing each letter of the mark (in the case of word or letter marks) *or otherwise indicating the description of the mark (in the case of marks in the form of a symbol or device or other nontextual form*). M.P.E.P. §608.01(v) (emphasis added). Applicant respectfully submits that the Deep Vent$_R$™ (exo-) (New England BioLabs) trademark used in this application has a fixed and definite meaning in the art. Previously, the specification was amended by either capitalizing each letter of each trademark (e.g., VENT) or by using the appropriate symbol to indicate a trademark (i.e., Deep Vent$_R$™). Accordingly, Applicant respectfully requests the Office to withdraw this objection.

III. Rejection Under 35 U.S.C. §112, First Paragraph

The Office rejects claims 1-11, 13, 15, 19, and 25-30 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not enable one of skill in the art to make and use the invention commensurate in scope with the claimed invention. Office Action at 5. The Office acknowledges that the specification enables the claimed subject matter for a range of pH from 9.3 to 10, but asserts that it "does not reasonably provide enablement for a range of pH 9.3 to 14." *Id.* Applicants respectfully traverse this rejection.

An Applicant's specification is ***presumptively enabled*** for the full scope of the claims. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971) (emphasis added); *accord*, M.P.E.P. § 2164.04. In fact, "[a]s a matter of Patent Office practice . . . [a specification] must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements." *In re Armbruster*, 185 USPQ 152, 153 (C.C.P.A. 1975).

The M.P.E.P. specifically states that the Office has the initial burden to establish a reasonable basis to question the enablement of the claimed invention. M.P.E.P. § 2164.04. This reasonable basis may be established by the Office by "making specific findings of fact, supported by evidence, and then drawing conclusions based on these findings of fact". . . "[h]owever, specific technical reasons are always required." *Id.* Absent such evidence, the burden does not shift to the Applicant. *In re Marzocchi*, 169 USPQ at 369.

The test of enablement is whether one of ordinary skill in the art could make the invention from the disclosure in the patent coupled with information known in the art without undue experimentation. M.P.E.P. § 2164.01. To determine whether experimentation is undue, the Office must apply the factors identified in the Federal Circuit's decision in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). M.P.E.P. § 2164.01(a). As detailed below in discussing a number of the *Wands* factors, the Office has failed to meet the burden imposed upon it by the M.P.E.P. and the prevailing case law.

A. Level of Skill in the Art

The Office deems that the level of skill in the art is high. *Id.* at 6. This factor weighs in favor of enablement.

B. Guidance in the Specification

The Office argues that the "specification provides no evidence that the disclosed protein fusion polymerase would be able to function in pH range of 10 to 14." *Id.* at 5. This is not true. Example 3 of the specification shows that Pfu-Sso7d fusions and polymerase blends comprising the same efficiently amplify DNA in reaction buffers with pH ranging from 9.5 to 12. *See* Specification at 80-82; *see also* Figures 1-6. Thus, contrary to the Office's position, the specification provides evidence and thus demonstrates that the fusion DNA polymerases operate well above pH 10.

C. Working Examples

The Office again asserts that the "specification has no working examples of synthesizing DNA in the pH range of 10 to 14 with a protein fusion polymerase." Office Action at 5. As noted above, Example 3 directly refutes the Office's position and demonstrates that the specification does provide working examples showing that the invention works as set forth in the specification.

D. Quantity of Experimentation

Citing U.S. Patent No. 4,545,933 ("the '933 patent"), the Office asserts that the "quantity of experimentation in this area is extremely large since there [*sic*] the art teaches that protein hydrolyses at pH 10 and higher." Office Action at 5. As an initial matter, the '933 patent is not directed to proteins generally, but rather, is directed specifically to a process for preparing hydrolyzed protein from *casein*. Moreover, Applicant's specification demonstrates that the fusion DNA polymerases of the invention function efficiently above pH 10. Thus, unlike the casein protein discussed in the '933 patent, the fusion DNA polymerases of the invention do not hydrolyze at pH 10. In fact, as noted above, the specification shows that the fusion DNA polymerases of the invention function throughout a wide range of alkaline buffers, including pH 9.5 to pH 12. Accordingly, given the guidance in the specification and the high level of skill in the art, the experimentation involved to test fusion DNA polymerases in reaction buffers with a pH above 12, and thus practice the full scope of the pending claims, would have been routine and well within the skill of those in the art. *See e.g.*, *Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1360, 47 USPQ2d 1705, 1719 (Fed. Cir. 1989) ("test [for undue experimentation] is not merely quantitative . . . if it is merely routine.").

E. Nature of Invention and Breadth of the Claims

The Office notes that independent claims 1, 6, 7, and 9 recite synthesizing DNA with a fusion protein in the pH range of 9.3 to 14 and asserts that "the specification does not disclose that the fusion polymerase will operate above pH 10." Id. As noted above, this is not true. The

specification provides working examples showing that the Pfu-Sso7d fusions and polymerase blends comprising the same efficiently amplify DNA in reaction buffers with a pH ranging from 9.5 to 12. Furthermore, the specification discloses that the fusion DNA polymerases and fusion DNA polymerase blends of the invention will work at a high pH (*i.e.*, 9.1 to 14). *See* Specification at 26, lines 17-23.

A review of the *Wands* factors demonstrates that the Office's attempt to establish at *prima facie* case of nonenablement rests on two faulty presumptions. The first faulty presumption is the Office's assertion that the specification does not disclose that the DNA fusion polymerase will operate above pH 10. The specification demonstrates otherwise. The second faulty assumption is the Office's reliance on the '933 patent to allegedly demonstrate that proteins, such as the claimed fusion DNA polymerases, will hydrolyze at pH above 10. As demonstrated by the working examples of this application, however, the fusion DNA polymerases operate efficiently at a pH well above 10. Therefore, the specific teaching about the hydrolysis of casein proteins in the '933 patent does not extend to the fusion DNA polymerases recited in the pending claims. Accordingly, in the absence of any sound technical reasons to support its enablement rejection, the Office has not met its initial burden to establish a reasonable basis to question the enablement of the claimed invention. For these reasons, Applicant respectfully requests that the Office reconsider and withdraw this enablement rejection of claims 1-11, 13, 15, 19, and 25-30.

IV. Rejections Under 35 U.S.C. § 103

A. *Wang* Does Not Render Claims 1-4, 7-11, 13, 15, 19, 25-30, and 40 Obvious

The Office rejects claims 1-4, 7-11, 13, 15, 19, 25-30, and 40 under 35 U.S.C. § 103(a) as allegedly obvious over WO 01/082501 (*Wang*). Office Action at 6. Applicant respectfully traverses this rejection.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See* M.P.E.P. § 2142. Applicant submits that *Wang*, alone, or in combination with the state of the art, do not teach all of the elements of the rejected claims. As acknowledged by the Office, "Wang does teach pH 8.8 but does not specifically teach the pH range of 9.3 to 10." *Id.* at 9. The Office asserts "it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention was made to use a pH in [*sic*, the] range of 9.3-10 as used by the applicant which is in the range of pH 8.8 as used by Wang, since these differences in pH would not be expected to greatly alter the conditions for amplification." *Id.* Applicant respectfully disagrees.

Wang discloses the standard reaction buffer for wild type Pfu polymerase, which contains 20 mM Tris-HCl (pH 8.8) as a buffering component. *Wang* similarly discloses the use of the same buffer with an additional 40 mM of KCl for Taq polymerase, a Pfu-Sso7d polymerase fusion, and an Sso7d-Taq polymerase fusion. This is consistent with the specification, which notes that the buffering component in standard PCR reaction buffers ranges from 8.3 – 8.8. *See* Specification at page 26, lines 21-23 and page 63, lines 20-21.

First, Applicant notes that if the buffering component in the standard PCR reaction ranges from 8.3 to 8.8, once the buffering component is added to the PCR reaction buffer, the final pH of the PCR reaction buffer will be slightly lower than the pH of the buffering component. Second, and more significantly, one of skill in the art of PCR enzymes would expect that using a Pfu DNA polymerase, or another standard polymerase, in a high pH buffer would negatively affect the efficiency of the polymerase. As the pH increases above 9, one of skill in the art would expect an inversely proportional reduction in the polymerase activity of standard DNA polymerases, such as Pfu. Thus, one of skill in the art would not be motivated to raise the conventional PCR reaction pH of around 8.5 to a pH of 9.3 or higher because he would expect that such a change would impair the polymerase activity of the polymerase enzyme. Accordingly, contrary to the Office's assertions, one of skill in the art of PCR enzymes would expect the differences between the conventional pH used for PCR and the pH recited in the pending claims to have a significant *negative* impact on polymerase activity.

Furthermore, Applicant has unexpectedly discovered that high pH enhances the amplification efficiency of Applicant's fusion DNA polymerases and blends comprising the same as shown, for example, by decreased extension times in PCR reactions. For example, as disclosed in the specification, the more processive Pfu-Sso7d fusion polymerase was able to amplify a 6kb human beta globin genomic target sequence with an extension time of 15 seconds per kb at high pH, whereas "*Pfu* Turbo [*i.e.*, wild type Pfu] alone cannot amplify this target at 15 seconds per kb." *See* Specification, page 80, lines 3-9. "Amplification [of the 6kb human beta

globin genomic target] appears at pH 8.5 and is strongest between pH 10-12, demonstrating the enhancing effect of high pH on the chimeric *Pfu*-Sso7d DNA polymerase (figures 1 & 2)." *Id.* at page 80, lines 9-10. In addition, Applicant demonstrated the superiority of its high pH buffers as compared with the state of the art Pfu buffer of *Wang*. More specifically, PCR amplifications using a blend comprising a Pfu-Sso7d fusion and pH 10 and 11.8 reaction buffers "were dramatically superior to the 1.5X cloned *Pfu* buffer, further demonstrating the enhancing effects of high pH for PCR amplification with *Pfu*-Sso7d (figure 3)." Specification at page 80, line 12 to page 81, line 2. These results also directly contradict the state of the art that teaches increasing the pH above 9 with standard polymerases, such as Pfu, reduces the efficiency of PCR amplification.

Accordingly, Applicant submits that *Wang*, alone, or in combination with the state of the art, fail to teach or suggest all elements of claims 1-4, 7-11, 13, 15, 19, 25-30, and 40 and, thus, do not render those claims obvious. For at least this reason, Applicant requests that the Office reconsider and withdraw the rejection of claims 1-4, 7-11, 13, 15, 19, 25-30, and 40 as unpatentable over *Wang*.

B. *Wang* in Combination with *Sanger* Does Not Render Claims 5 and 6 Obvious

The Office rejects claims 5 and 6 under 35 U.S.C. § 103(a) as allegedly obvious over *Wang* in combination with *Sanger*. Office Action at 11. Applicant respectfully traverses this rejection.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See* M.P.E.P. § 2142. Applicant submits that the combined teachings of the cited references do not teach all of the elements of the rejected claims. For the reasons discussed above, *Wang* fails to teach or suggest a pH from 9.3 to 14. *Sanger* also fails to teach or suggest this element of the claims and thus fails to remedy the deficiencies of *Wang*.

Accordingly, Applicant submits that the combined teachings of *Wang* and *Sanger* fail to teach or suggest all elements of claims 5 and 6 and, thus, do not render those claims obvious. For at least this reason, Applicant requests that the Office reconsider and withdraw the rejection of claims 5 and 6 as unpatentable over the combination of these references.

V. Conclusion

Applicant believes that all of the substantive issues raised in the Final Office Action mailed 17 August 2007 have been addressed, and all objections and rejections overcome. Accordingly, Applicant believes that this application is in condition for allowance. If the Office believes anything further is required in order to place this application in even better condition for allowance, Applicant requests that its undersigned representative be contacted at the number listed below to discuss remaining issues.

Please grant any extensions of time required to enter this paper and charge any additional required fees to Deposit Account No. 50-3740.

Respectfully submitted,
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